CASE REPORT

Gonadotropin-releasing hormone agonist against severe aggression in autism

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Accepted 5 September 2016

SUMMARY

Aggression in patients with autism spectrum disorder (ASD) presents an important therapeutic challenge. Conventional treatment appears to be inadequate in a number of cases. The occurrence of severe aggressive symptoms since the inception of adolescence in a male patient with ASD suggested a hormonal influence by androgens. Conventional treatment with antipsychotic and antiepileptic drugs and benzodiazepines was ineffective. A subcutaneous long-acting gonadotropin-releasing hormone agonist (GnRH agonist) injection was given on a monthly basis resulting in a substantial improvement in his aggressive behaviour and renewed socialisation.

BACKGROUND

Aggressive behaviour in patients with autism spectrum disorder (ASD)[1] constitutes a major problem and nearly always has a great impact on the well-being of the patient, the close relatives and environment. Intellectual disability and aggressive behaviour are often found in patients with ASD and antipsychotic drugs are predominantly used to temper aggressive outbursts.[2 3] No beneficial effect of antipsychotic drugs on aggressive behaviour in patients with intellectual disability was found in a randomised controlled trial comparing antipsychotic drugs with placebo.[3] Alternative treatment options should be investigated for alleviating the symptoms since the effectiveness of a standard psychopharmacological treatment appears to be uncertain. Gonadotropin-releasing hormone agonists (GnRH agonists) could be a rational treatment option. A PubMed and Embase search was conducted with the following entries: (1) GnRH and psychiatry, (2) GnRH and autism, (3) GnRH and aggression, (4) GnRH and aggressive behavior, (5) Autism and aggression and hormonal treatment, (6) Hormonal treatment and aggression, (7) Hormonal treatment and autism, (8) Antihormones and aggression and (9) Antihormones and autism. This revealed a publication on the beneficial effects of prolonged GnRH agonists' administration in six adult men with obsessive–compulsive disorder.[4] After the publication of this trial, the author (TE) also used GnRH agonists in adult patients with ASD with favourable results on aggressive symptoms.

CASE PRESENTATION

Severe aggressive behaviour started during late adolescence in a patient diagnosed with ASD at the age of 2 years, causing automutilation and injuries of family members and supervisors. Permanent institutionalisation became inevitable with long periods of solitary confinement and a three-to-one surveillance during the sparse activities. The diagnosis of ASD was based on the following diagnostic criteria: (1) persistent deficits in social communication and social interaction, (2) restricted, repetitive patterns of behaviour, interests and activities, (3) the occurrence of symptoms in the early developmental period and (4) a significant impairment in everyday social and occupational functioning.[1] Mental status examination indicated intellectual disability. An IQ of 75 was calculated. However, this figure has to be considered with reservation because of the discordant composition of intelligence in these patients. The earlier mentioned symptoms exceeded difficulties expected on the basis of developmental level increasing the uneven profile of abilities. The use of single words only, often intelligible, and the extreme difficulties in the use of language for reciprocal social communication indicated severe language impairment. Intellectual impairment and language impairment were comorbid diagnoses.[1]

Antipsychotic drugs (especially pipamperone, risperidone and quetiapine), antiepileptic drugs (valproic acid) as 'mood stabilisers' and benzodiazepines (temazepam and lorazepam) were administered for several years in the following daily dosages: pipamperone 80 mg, risperidone 2 mg, quetiapine 25 mg, valproic acid 1200 mg, temazepam 20 mg and lorazepam 7.5 mg.

Adverse effects such as parkinsonism, tardive dyskinesia, urine incontinence, and eating and sleep disorders were observed and opposed increasing the dosages of the antipsychotic drugs and benzodiazepines. A creatine deficiency syndrome, due to a creatine transporter gene *SLC6AB*; Xq28 mutation[5] which might explain the serious side effects, was excluded. The aggressive symptoms did not diminish under the above-mentioned treatment protocol. The negative balance between effectiveness and adverse effects lead to discussions on alternative approaches.

A hormonal involvement, especially an androgenic influence, seemed plausible since the deterioration started during puberty. Central downregulation with GnRH agonists is the most effective treatment option for achieving lower androgen levels. The effects are reversible after discontinuation and the most important side effect, bone density loss, can be measured and treated.

Following consultation of the Royal Dutch Medical Association, the Dutch Health Care Inspectorate and the Dutch Central Committee for

To cite: van der Weiden RMF, Helmerhorst FM, Eriksson T. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2016-216378

Human Research, a treatment protocol with GnRH agonists was drafted. The protocol met the requirements for the off-label prescription of medicines as meticulous documentation, the possibility of consulting a pharmacist, the exploration of alternatives and a careful consideration of the risks involved. The Dutch Medicines Evaluation Board even ascertains that it is the duty of a physician to prescribe off-label drugs when there is a rational proof for effectiveness and when the specific drug appears to be the best treatment option. An advisory board was instituted consisting of the attending physician of the institute, a reproductive endocrinologist, a hospital pharmacist and a consultant psychiatrist. The frequency and intensity of aggressive outbursts and eventual complications of treatment were documented. At the start of treatment, the patient was 26 years of age. Baseline testosterone and sex hormone-binding globulin levels were normal.

INVESTIGATIONS

The following additional investigations were performed: EEG to exclude epileptic disorders, cerebral CT scan, dynamic cerebral MRI, chromosome analysis to exclude abnormalities such as fragile X-syndrome and screening on metabolic disorders. No abnormalities were found.

DIFFERENTIAL DIAGNOSIS

The presence of symptoms at an early age, the impaired social reciprocity and the preference for repetitive patterns of behaviour excluded selective mutism, language disorders and social (pragmatic) communication disorder. Owing to the discrepancy between the level of social-communicative skills and other intellectual skills, the diagnosis of ASD supersedes the diagnosis of intellectual developmental disorder. The diagnosis of attention-deficit/hyperactivity disorder was not appropriate since hyperactivity was not a predominant feature. The absence of hallucinations and delusions excluded schizophrenia with childhood onset.[1]

TREATMENT

After a stepwise diminution and eventual cessation of all psychopharmacological drugs, treatment was started with a monthly ready-made subcutaneous injection of the long-acting GnRH agonist triptorelin 3.75 mg (Decapeptyl Depot, Ferring, Kiel, Germany), as described earlier.[4]

OUTCOME AND FOLLOW-UP

During the first months of treatment, the number and intensity of the aggressive incidents gradually diminished; after 6 months of treatment, the patient could visit his parental home for a few hours, the first visit home in 3 years. Several months later, the parents could join the patient in a number of activities without any surveillance and the visits home became more frequent and were lengthened in duration to complete weekends after 1.5 years, from the start of the monthly GnRH agonist injections. Bone mineral density measurement after 1 year of treatment indicated osteopenia and alendronic acid, vitamin D and calcium were started. A slight gynaecomastia and the absence of sexual responses were also observed. After 2 years of treatment, the patient could be transferred to another institute, closer to the parental home and with a significantly less stringent regime and a meaningful type of day care. The GnRH agonist, initially started to break a stalemate situation, was given bimonthly at this time without any change in the situation. Bone mineral density remains stable. The effects of a further diminution and finally of a cessation of treatment are uncertain.

DISCUSSION

This case report describes an alternative treatment option against aggressive symptoms in patients with ASD. We are fully aware of bias; however, in this particular case, a remarkable amelioration was observed with long-acting GnRH agonists.

There are a number of papers about treating aggression with hormones, but we found only one relevant paper (plus the additional personal information by the author) on the subject of this case report: prolonged administration of a long-acting GnRH agonist in a patient with ASD and aggression.[4]

In the past, an antiaggressive effect of cyproterone acetate was mentioned in a brief report on three neuroleptic refractory aggressive male patients. These were no patients with ASD.[6] We decided not to use cyproterone acetate after considering the balance between effectiveness and (additional) side effects, particularly hepatotoxicity, of cyproterone acetate relative to GnRH agonists.

The documented use of GnRH agonists in autism refers to the suppression of deviant sexual behaviour.[7] The authors reported a follow-up in patients using GnRH agonists for almost 3 years with no abnormal physical effects.[7] This is in accordance with our experience and the experience of Eriksson[4] reported after 2 years of treatment. Prospective controlled trials on long-acting GnRH agonists for the suppression of deviant sexual behaviour were not found in a recent Cochrane Database search.[8]

A positive effect of combined long-acting GnRH agonist and antiheavy metal therapy on (aggressive) behaviour was reported after 3 months of treatment in 11 children with ASD and elevated androgens, in comparison to their age-specific and sex-specific reference range.[9 10] The median age was only 9 years and patients were treated for up to 7 months. The rationale for this approach would be the effect of androgens on mercury levels; reducing androgens would reduce the effects of mercury. Mercury could, theoretically, impair neuronal development,[9 10] but the proposed interaction between androgens and mercury is speculative.[9–11] There are no studies which indicate that mercury causes autism.[11] The beneficial effects observed in this trial[9] might be (predominantly) the result of the GnRH agonist. A consensus statement on the use of GnRH agonists in children was published a few years after this controversial paper: GnRH agonists should not be given to children as pubertal suppression interrupts natural processes.[12 13]

Baseline androgen levels in our 26-year-old patient were not elevated and a significant reduction in symptoms was observed after 6 months of long-acting GnRH agonist treatment as a single medication.

We decided to use the GnRH agonist triptorelin because of the experiences reported earlier.[4] Leuproreline 3.75 mg (Lucrin Depot, Abbott, Madrid, Spain), also a ready-made subcutaneous injection, can be used for the same purpose.

In conclusion, this is the first published case on successful long-acting GnRH agonist administration against aggression in an autistic patient with normal baseline androgens. At this moment, research on novel medications in patients with ASD does not include the use of GnRH agonists.[14] The long-acting GnRH agonist treatment strategy deserves more attention, preferably in a randomised controlled setting.

Patient's perspective

- This case report describes the remarkable effects of long-acting gonadotropin-releasing hormone agonist administration in a hopeless situation and presents an issue of concern and interest to other patients with autism spectrum disorder severely hampered by aggressive behaviour.
- RMF vdW, father of the patient (and first author of this case report).

Learning points

- Aggressive behaviour in (male) patients with autism spectrum disorder is a common and major problem.
- Antipsychotic drugs are predominantly used, with insufficient effect in a number of cases.
- Lowering of androgen levels by a long-acting gonadotropin-releasing hormone agonist can be effective in these cases.
- The effects of gonadotropin-releasing hormone agonists are reversible. The side effects can be measured and treated.

Author note An earlier, abridged, version of this paper has been published in *Medisch Contact* 2015;70:1284–5.

Contributors RMFvdW made substantial contributions to conception and design, acquisition of data and analysis and interpretation of data; drafted the manuscript and revised it critically for important intellectual content; and has given final approval of the version to be published. FMH made substantial contributions to conception and design, acquisition of data and analysis and interpretation of data; has been involved in revising the manuscript critically for important intellectual content; and has given final approval of the version to be published. TE made substantial contributions to conception and design, acquisition of data and analysis and interpretation of data and supervised the experiment. TE deceased in 2014. The family has given permission to add TE as a coauthor.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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